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PROVISIONAL SPECIFICATION

for the invention entitled:

“Therapeutic cellular agents”

The invention is described in the following statement:

THERAPEUTIC CELLULAR AGENTS

FIELD OF THE INVENTION

5 The present invention relates to a method for inducing development of blood dendritic cells from CD34⁺ precursor cells. More particularly, the present invention provides a protocol for the development of blood dendritic cells from *inter alia* cord blood, bone marrow or peripheral blood CD34⁺ stem cells. The blood dendritic cells of the present invention are useful as therapeutic cellular agents such as in the development of vaccines
10 and in modulating immunological responsiveness.

BACKGROUND OF THE INVENTION

Bibliographic details of references provided in the subject specification are listed at the end
15 of the specification.

Reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that this prior art forms part of the common general knowledge in any country.

20

Dendritic cells (DC) are potent cellular activators of primary immune responses (Hart, *Blood* 90: 3245-3287, 1997). Immature myeloid DC in non-lymphoid organs react to endocytose and process antigens and migrate *via* blood and lymph to T cell areas of lymphoid organs. Here, the mature cells present foreign peptide complexed to MHC Class
25 I and II to T cells and deliver unique signals for T-cell activation (immuno-stimulation). They also stimulate B lymphocytes and NK cells. DC undergo differentiation /activation during this process, lose their antigen-capturing capacity and become mature, immuno-stimulatory DC that trigger naïve T-cells recirculating through the lymphoid organs. The lymphoid DC subset may have a different migration pathway and although capable of
30 stimulating allogeneic and autologous T-lymphocytes they have been suggested to have a regulatory function (Grouard *et al.*, *J. Exp. Med.* 185: 1101-1111, 1997). As part of the

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differentiation/activation process, DCs up-regulate certain relatively selectively-expressed cell surface molecules such as the CMRF-44 and CD83 antigens. DC in the thymus and blood that do not have an activated co-stimulating phenotype probably contribute to central and peripheral tolerance.

5

Blood dendritic cells (BDC) are released from bone marrow into the peripheral blood before homing to the tissues as surveillance DC for the immune system. The two major subsets of BDC are myeloid DC (CD11c⁺ CD123^{-dim}) and lymphoid (CD123^{hi} CD11c⁻).

- 10 There is a need to develop a protocol for generating BDC and in particular myeloid BDC and lymphoid BDC sub-populations. Such cells are useful as potential cellular agents for use, for example, in the manufacture of vaccines or in modulating immunological responsiveness. However, DC circulate in low number in the peripheral blood system and are, hence, difficult to isolate. A protocol is required, therefore, to generate a ready source
- 15 of BDC.

SUMMARY OF THE INVENTION

Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element or integer or group of elements or integers but not the exclusion of any other element or integer or group of elements or integers.

The present invention provides a method for inducing or otherwise facilitating development of blood dendritic cells (BDC) from CD34⁺ precursor cells. Generally, the CD34⁺ precursor cells are from sources such as cord blood, bone marrow or peripheral blood. Cord blood is particularly preferred. The protocol generally involves sorting CD34⁺ precursor cells into a myeloid population and/or a lymphoid population. The myeloid population is generally CD33⁺CD7⁺CD10⁻ and the lymphoid population is generally CD33⁺CD7⁺CD10⁺. One or both sub-populations of CD34⁺ precursor cells are then cultured into the presence of one or more cytokines and preferably a cocktail of cytokines for a time and under conditions sufficient for CD34⁺-derived DC to develop. The myeloid DC precursors differentiate *via* either CD14 or CD1a pathways. Within the expanded population, monocytes (CD14⁺), granulocytes (CD15⁺), myeloid BDC-like cells (CD11c⁺CD123⁻) and lymphoid BDC-like cells (CD11c⁻CD123^{hi}) may develop. The latter myeloid and lymphoid BDC are proposed to be potential therapeutic cellular agents for the development of vaccines and to modulate immunological responsiveness.

The present invention provides, therefore, a method for generating myeloid- or lymphoid-like BDC, said method comprising isolating CD34⁺ precursor cells, sorting into a myeloid and/or lymphoid population and culturing either or both populations in the presence of one or more cytokines or functional, recombinant or chemical homologs or equivalents thereof for a time and under conditions sufficient for CD34⁺ cell expansion to occur and then isolating the CD34⁺-derived myeloid- or lymphoid-like BDC.

The useful cytokines are, for example, flt3, SCF, IL-3, IL-6, GM-CSF, G-CSF and/or TNF α .

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The ability to enrich for, or generate, myeloid- or lymphoid-like BDC permits a marked improvement over monocyte-derived DC. The isolated cells may be used to generate vaccines to induce an immunological response against specific antigens or may be used to
5 induce immunological tolerance or non-responsiveness.

The present invention provides, therefore, an isolated population of lymphoid- or myeloid-like BDC for use in vaccine development or as potential therapeutic cellular agents to, for example, induce immunological tolerance or non-responsiveness.

10

The present invention further contemplates the use of myeloid- or lymphoid-like BDC derived from CD34⁺ precursor cells in the manufacture of a population of potential therapeutic cellular agents.

15 The present invention also provides vaccines comprising the isolated myeloid- or lymphoid-like BDC loaded with particular antigens.

Reference to a "CD" includes a "CD^{lo}" or "CD^{hi}" marker.

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BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a graphical representation showing the growth of cord blood (CB) CD34⁺ myeloid precursors in the presence of flt3, SCF, IL-3 and IL-6 to generate an expanded
5 culture.

Figure 2 is a graphical representation showing the emergence of CD14⁺ progeny.

Figure 3 is a graphical representation showing the emergence of CD15⁺ progeny.
10

Figure 4 is a graphical representation showing the emergence of CD14⁻ CD15⁻ progeny.

Figures 5(A)-(E) are graphical representations of CD11c⁺ DC's existing in a CD14⁻ CD15⁻ population after precursor cell expansion.
15

Figure 6 is a graphical representation showing that CD11c⁺HLA-DR⁺CD123⁻CD1a⁻ cells can induce a potential mixed lymphocyte reaction (MLR).

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides a protocol for developing myeloid- or lymphoid-like BDC form CD34⁺ precursor cells. Reference herein to "myeloid-like BDC" and "lymphoid-like
5 BDC" includes myeloid BDC and lymphoid BDC, respectively.

Myeloid-like BDC have the potential for inducing more potent allogenic T-lymphocyte responses compared to granulocytes or monocytes and, hence, are proposed to be useful therapeutic cellular agents in the development of vaccines and to modulate immunological
10 responsiveness.

Accordingly, one aspect of the present invention contemplates a method for generating a population of myeloid- or lymphoid-like BDC, said method comprising obtaining a population or source of CD34⁺ precursor cells, sorting this population into myeloid and/or
15 lymphoid precursors, culturing either or both populations with one or more cytokines for a time and under conditions sufficient to obtain a CD34⁺-derived cell expansion culture and then isolating myeloid-like BDC or lymphoid-like BDC from the expanded cell culture.

The CD34⁺ precursor cells are preferably CD34⁺ stem cells from any convenient source.
20 The most convenient source is cord blood. Other sources include bone marrow and peripheral blood.

In relation to these preferred sources of CD34⁺ precursor cells, another aspect of the present invention provides a method for generating a population of myeloid- or lymphoid-
25 like BDC, said method comprising obtaining a population or source of CD34⁺ stem cells from cord blood, bone marrow and/or peripheral blood sorting this population into myeloid and/or lymphoid precursors, culturing either or both populations with one or more cytokines for a time and under conditions sufficient to obtain a CD34⁺-derived cell expansion culture and then isolating myeloid-like BDC or lymphoid-like BDC from the
30 expanded cell culture.

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By "obtaining" CD34⁺ precursor cells including stem cells means enriching, selecting and/or isolating CD34⁺ cells from mixed populations of cells. The CD34⁺ precursor cell culture does not have to be pure or solely or substantially CD34⁺ cells but a substantially homologous population of CD34⁺ cells is certainly preferred. The present invention
5 extends, however, to heterogenous mixtures of cells provided the mixture comprises CD34⁺ precursor-cells and in particular CD34⁺ stem cells. Sorting of the CD34⁺ precursor cells provides a population of myeloid precursors having characteristic markers CD33⁺CD7⁻CD10⁻ and a population of CD33^{+/+}CD7⁺CD10⁺ lymphoid precursors. Either or both populations may then be subject to expansion-enhancing conditions. Although either
10 myeloid or lymphoid precursor CD34⁺ cells may be employed in the practice of the present invention, up to the present time, myeloid precursor cells are particularly preferred. Myeloid precursor CD34⁺ cells give rise to myeloid-like BDC which are CD11c⁺CD123⁻ cells. Lymphoid precursor CD34⁺ cells have the potential to give rise to lymphoid-like BDC which are CD11c⁻CD123^{hi}. Conveniently, CD34⁺ cells may be collected by any
15 convenient means such as being immobilized to magnetic particles or FACS sorting microspheres.

Sorting is preferably conducted with a flow cytometer which comprises a "fluorescence-activated cell sorter" (FACS) [see, for example, "Methods in Cell Biology" Vol. 33,
20 Darzynkiewica, Z. and Crissman, H.A., eds., Academic Press) and Dengl and Herzenberg, *J. Immunol. Methods* 52: 1-14, 1982].

Accordingly, in a preferred embodiment, the present invention contemplates a method for generating a population of myeloid-like BDC, said method comprising obtaining a
25 population or source of CD34⁺ precursor cells, sorting this population to obtain myeloid precursor cells characterized by being CD33⁺CD7⁻CD10⁻, culturing this population with one or more cytokines for a time and under conditions sufficient to obtain a CD34⁺-derived cell expansion culture and then isolating myeloid-like BDC characterized by being CD11c⁺CD123⁻ from the expanded cell culture.

30

Preferably, the CD34⁺ precursor cells are derived or obtained from cord blood. However,

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precursor cells from bone marrow and/or peripheral blood are also contemplated by the present invention.

5 The CD34⁺ cell expansion conditions include incubating or culturing the cells in the presence of one or more cytokines. Preferably, a cocktail of two or more cytokines is employed. Although a range of cytokines may be employed, particularly useful cytokines are those selected from flt3, SCF, IL-3 and IL-6 or their functional, recombinant or chemical equivalents or homologs. Other useful cytokines include GM-CSF, G-CSF and TNF α .

10

Accordingly, another aspect of the present invention contemplates a method for generating a population of myeloid- or lymphoid-like BDC, said method comprising obtaining a population or source of CD34⁺ precursor cells, sorting this population into myeloid and/or lymphoid precursors, culturing either or both populations with one or more cytokines
15 selected from flt3, SCF, IL-3, IL-6, GM-CSF, G-CSF and TNF α or their functional, recombinant or chemical equivalents or homologs for a time and under conditions sufficient to obtain a CD34⁺-derived cell expansion culture and then isolating myeloid-like BDC or lymphoid-like BDC from the expanded cell culture.

20 Preferably, the CD34⁺ precursor cells are CD34⁺ cord blood-derived stem cells. Even more preferably, the cells generated are myeloid-like BDC characterized by being CD11c⁺CD123⁻.

A range of cytokines or functional equivalents may be employed and the present invention
25 extends to any and all conditions which facilitate cell expansion. In a most preferred embodiment, however, a cocktail of cytokines comprising flt3, SCF, IL-3 and IL-6 is employed.

Accordingly, another aspect of the present invention contemplates a method for generating
30 a population of myeloid- or lymphoid-like BDC, said method comprising obtaining a population or source of CD34⁺ precursor cells, sorting this population into myeloid and/or

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lymphoid precursors, culturing either or both populations with a mixture of cytokines comprising flt3, SCF, IL-3 and IL-6 or their functional, recombinant or chemical equivalents or homologs of any or all of the above for a time and under conditions sufficient to obtain a CD34⁺-derived cell expansion culture and then isolating myeloid-like
5 BDC or lymphoid-like BDC from the expanded cell culture.

In another preferred embodiment, the present invention provides a method for generating a population of myeloid- or lymphoid-like BDC, said method comprising obtaining a population or source of CD34⁺ stem cells from cord blood, bone marrow and/or peripheral
10 blood, sorting this population into myeloid and/or lymphoid precursors, culturing either or both populations with a mixture of cytokines comprising flt3, SCF, IL-3 and IL-6 and optionally one or more of GM-CSF, G-CSF and TNF α or their functional, recombinant or chemical equivalents or homologs of any or all of the above for a time and under conditions sufficient to obtain a CD34⁺-derived cell expansion culture and then isolating
15 myeloid-like BDC or lymphoid-like BDC from the expanded cell culture.

In yet another embodiment, the present invention contemplates a method for generating a population of myeloid-like BDC, said method comprising obtaining a population or source of CD34⁺ precursor cells, sorting this population to obtain myeloid precursor cells
20 characterized by being CD33⁺CD7⁺CD10⁻, culturing both populations with a mixture of cytokines comprising flt3, SCF, IL-3 and IL-6 and optionally one or more of GM-CSF, G-CSF and TNF α or their functional, recombinant or chemical equivalents or homologs of any or all of the above for a time and under conditions sufficient to obtain a CD34⁺-derived cell expansion culture and then isolating myeloid-like BDC characterized by being
25 CD11c⁺CD123⁻ from the expanded cell culture.

The myeloid- and lymphoid-like BDC populations obtainable by the method of the present invention are proposed to be useful in the generation of vaccines and to modulate immunological responsiveness.

30

The present invention provides, therefore, a population of cells comprising myeloid- or

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lymphoid-like BDC, said population of cells isolated or enriched from an expanded culture of CD34⁺ cells generated from myeloid or lymphoid precursor cells sorted from a population of CD34⁺ precursor cells and cultured in the presence of one or more cytokines.

- 5 Reference to a "population" includes reference to an isolated culture comprising a homogenous, a substantially homogenous or a heterogenous culture of cells. Preferably, the population of myeloid-or lymphoid-like cells is substantially homogenous for one or either of these types of cells. Generally, a "popluation" may also be regarded as an "isolated" culture of cells.

10

In a preferred embodiment, a cocktail of cytokines is used comprising two or more of flt3, SCF, IL-3 and/or IL-6 or functional, recombinant or chemical equivalents thereof. Even more preferably, a cocktail comprises at least all of the flt3 ligand, SCF, IL-3 and IL-6.

- 15 In a particularly preferred embodiment, the present invention further extends to a population of myeloid-like BDCs, said population generated by the method of obtaining a population or source of CD34⁺ precursor cells, sorting this population into myeloid and/or lymphoid precursors, culturing either or both populations with one or more cytokines selected from flt3, SCF, IL-3 and IL-6 and optionally one or more of GM-CSF, G-CSF n
20 TNF α or their functional, recombinant or chemical equivalents or homologs for a time and under conditions sufficient to obtain a CD34⁺-derived cell expansion culture and then isolating myeloid-like BDC or lymphoid-like BDC from the expanded cell culture.

- The isolated, population of myeloid- and/or lymphoid-like cells are useful in the
25 manufacture of vaccines. In one embodiment, the cells are exposed, incubated or cultured with one or more antigens for a time and under conditions for the antigen to be taken up by the cells. Upon re-introduction of the antigen-load myeloid- or lymphoid-like BDC, an immune response is generated against the antigens. These antigens may be derived from pathogenic, microorganisms, parasites, cancer cells or other sources.

30

Vaccines are also useful in the treatment or prophylaxis of inflammatory bowel disease and

to increase levels of immune responsiveness such as during stress (e.g. surgery) or chemotherapy.

Alternatively, the myeloid- or lymphoid-like BDC may be loaded with sub-optimal levels
5 of antigen or loaded with a super dose which can result in the induction of immuno-
tolerance or immuno-non-responsiveness.

Accordingly, another aspect of the present invention contemplates a method of vaccinating
a subject against an antigen including a cell carrying the antigen, said method comprising
10 loading a myeloid- or lymphoid-like BDC with an amount of said antigen which will
induce an immune response wherein said myeloid- or lymphoid-like BDC or its parent is
prepared by the method of generating a population of lymphoid- or myeloid-like BDC,
said method comprising obtaining a population or source of CD34⁺ precursor cells, sorting
this population into myeloid and/or lymphoid precursors, culturing either or both
15 populations with one or more cytokines for a time and under conditions sufficient to obtain
a CD34⁺-derived cell expansion culture and then isolating myeloid-like BDC or lymphoid-
like BDC from the expanded cell culture.

Preferably, the CD34⁺ precursor cells are CD34⁺ stem cells from cord blood.
20

Preferably, the myeloid and/or lymphoid precursor cells are cultured in the presence of a
cytokine selected from the list comprising flt3, SCF, IL-3 and IL-6. Even more preferably,
the cells are cultured in a cocktail of cytokines comprising flt3-ligand, SCF, IL-3 and IL-6.
Other cytokines in the cocktail may optionally include GM-CSF, G-CSF and TNF α .

25 In a most preferred embodiment, the present invention contemplates a method of
vaccinating a subject against an antigen including a cell carrying the antigen, said method
comprising loading a myeloid-like BDC with an amount of said antigen which will induce
an immune response wherein said myeloid-like BDC or its parent is prepared by the
30 method of generating a population of myeloid-like BDC by obtaining a population or
source of CD34⁺ precursor cells, sorting this population into myeloid precursors, culturing

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this population with one or more cytokines for a time and under conditions sufficient to obtain a CD34⁺-derived cell expansion culture, loading the myeloid-like BDC with an antigen and then introducing the BDC to the subject. Generally, the subject is the source of the CD34⁺ precursor cells.

5

In another embodiment, as indicated above, the myeloid- or lymphoid-like BDC are loaded with sub-optimal or excess doses of antigen to induce immuno-tolerance or non-responsiveness.

- 10 The present invention provides, therefore, compositions for modulating the immune system or a response thereby, said composition comprising a myeloid- or lymphoid-like BDC generated by the method as hereinbefore described or are progeny cells of these generated cells. Such cells may be optionally loaded with antigen to induce a protective immune response or with sub- or over-optimum levels to induce immuno-tolerance or non-
15 responsiveness.

Generally, although not exclusively, when used in therapy, autologous BDC are used relative to the subject.

- 20 The preferred subject is a human but the present invention extends to other primates, livestock animals (e.g. sheep, cows, horses, pigs, donkeys, goats), companion animals (e.g. dogs, cats) or laboratory test animals (e.g. mice, rabbits, guinea pigs, hamsters) and avian species (e.g. chickens, game birds or aviary birds).

- 25 The present invention further contemplates the use of myeloid- or lymphoid-like BDC generated as hereinbefore described in the manufacture of a vaccine or therapeutic cellular agent.

Such a vaccine or therapeutic cellular agent is also regarded herein as a medicament.

30

In one embodiment, the vaccine or therapeutic cellular agent is useful for the treatment or

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prophylaxis of cancer infection by pathogenic microorganism, parasite or virus or to induce immuno-tolerance or non-responsiveness such as in the treatment or prophylaxis of autoimmune disease conditions.

- 5 The present invention is further described by the following non-limiting Examples.

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EXAMPLE 1

Generation of myeloid-like BDC

Sorted myeloid ($CD33^+CD7^-CD10^-$) and lymphoid ($CD34^+CD33^{+/ -}CD7^+CD10^+$) precursors from enriched cord blood $CD34^+$ cells were cultured in 24-well plates ($4-5 \times 10^4$ cells/ml) in H2000 serum free medium supplemented with a cocktail of cytokines (flt3-ligand 50 ng/ml, SCF 50 ng/ml, IL-3 10 ng/ml and IL-6 10 ng/ml) for 2-3 weeks. Figure 1 shows the growth of cord blood $CD34^+$ precursors in the presence of the cytokines. The progeny were assessed for phenotype on days 6-8 and every second day thereafter and also for their capacity to induce allogeneic T lymphocyte responses on days 8-12, of culture.

The presence of $CD11c^+$ myeloid-like BDC in a $CD14^-CD15^-$ population is shown in Figures 5A-E.

Figures 2-4 show the emergence of $CD14^+$, $CD15^+$ and $CD14^-CD15^-$ populations and Figure 5 shows the emergency of $CD11c^+CD14^-CD15^-$ progeny.

Figure 6 shows $CD11c^+HLA-DR^+CD123^-CD1a^-$ cells can induce a mixed lymphocyte reaction (MLR).

20

Peak $CD34^+$ derived cell expansion was observed on day 10-13 of culture, resulting in a 70 to 100 fold increase in cell number. Thereafter, cell number decreased steadily, although viable cells (>60%) could be observed for up to 3 weeks. There was no evidence of lineage differentiation during the initial period (4-6 days) of cell expansion. Monocytes ($CD14^+$ cells), granulocytes ($CD15^+$ cells), and myeloid-like BDC ($CD11c^+CD123^-$ cells) appeared subsequently (days 6-8) and were maintained during the period of culture. Only the $CD11c^+CD123^-$ progeny were capable of inducing potent allogeneic T lymphocyte responses, compare to monocytes and granulocytes.

25

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EXAMPLE 2***Yield of CD34⁺, myeloid/lymphoid precursors***

The yield of CD34⁺, myeloid/lymphoid precursor is shown in Table 1.

5

TABLE 1

Sample	Volume	MNC	CD34 ⁺	Myeloid precursor	Lymphoid precursor
CB 20	50 ml	350 x 10 ⁶	5.8 x 10 ⁶	0.6 x 10 ⁶	0.12 x 10 ⁶
CB 53	50 ml	300 x 10 ⁶	4 x 10 ⁶	0.5 x 10 ⁶	0.02 x 10 ⁶
CB 56	55 ml	310 x 10 ⁶	3.5 x 10 ⁶	0.3 x 10 ⁶	0.04 x 10 ⁶
CB 30*	-	360 x 10 ⁶	1.8-2.5 x 10 ⁶	-	-

Purity CD34⁺ cells: >98%

10

* Pranke, *Acta Haematologica* 105: 71-76, 2001

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood
 15 that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

- 16 -

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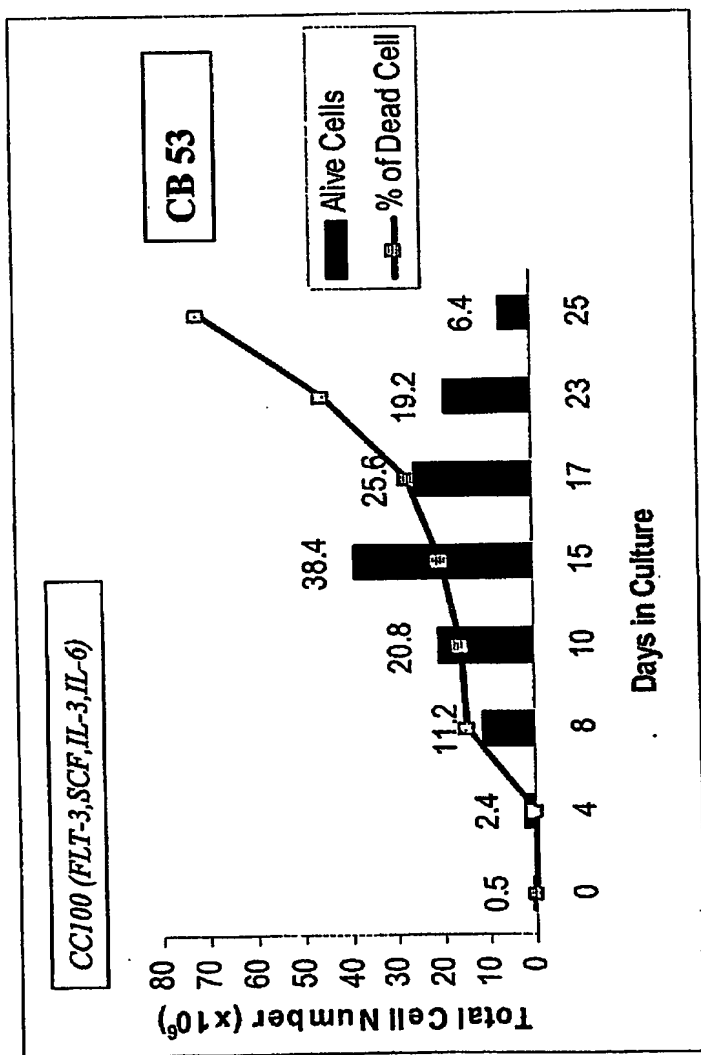
Grouard *et al.*, *J. Exp. Med.* 185: 1101-1111, 1997.

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DATED this thirtieth day of August 2002.

The Corporation of the Trustees of the Order of the Sisters of Mercy in Queensland
by DAVIES COLLISION CAVE
Patent Attorneys for the Applicant



Similar results from 4 exp.

*All Data derived from myeloid precursor

Figure 1

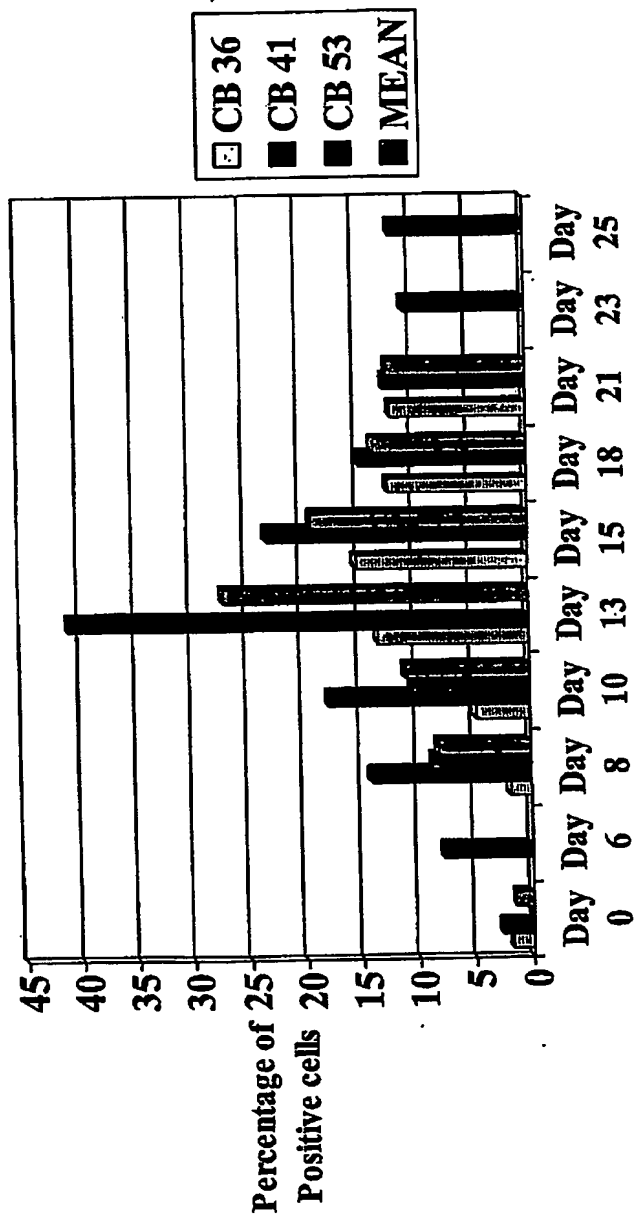
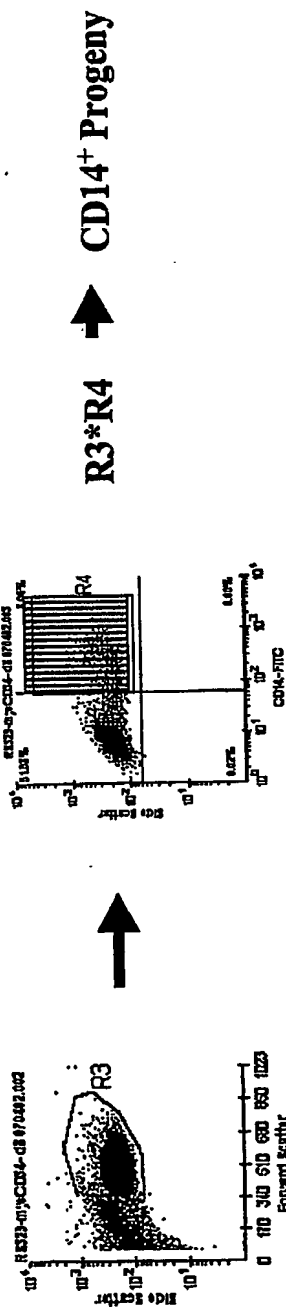


Figure 2

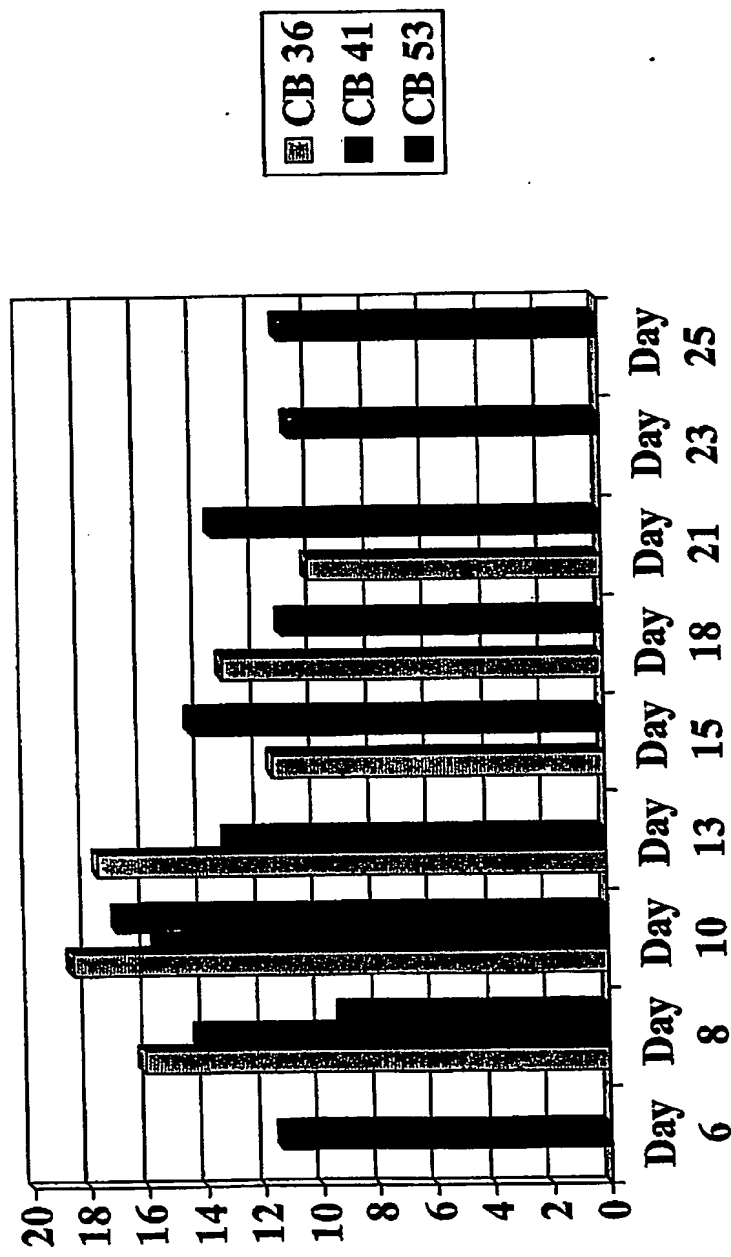


Figure 3

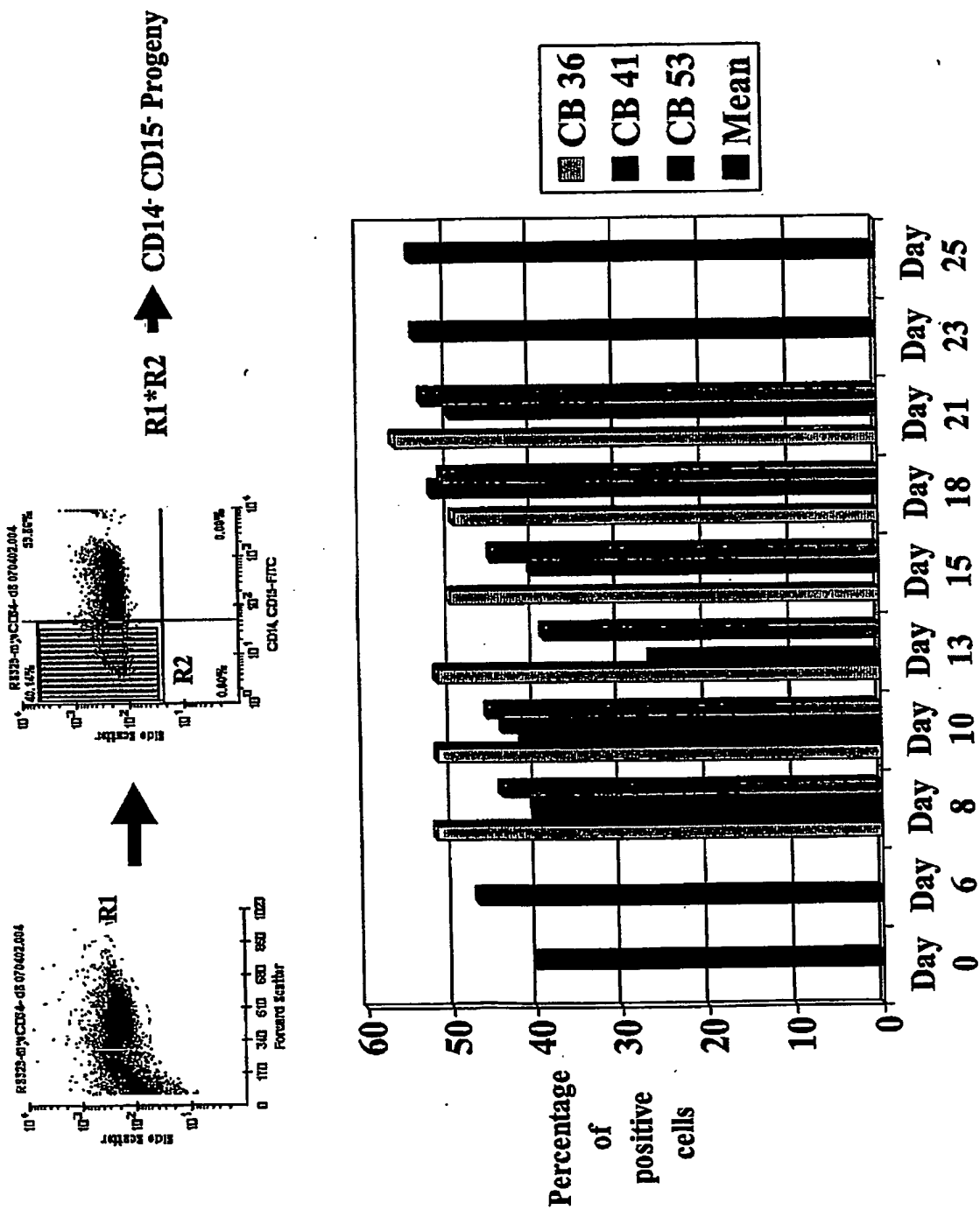


Figure 4

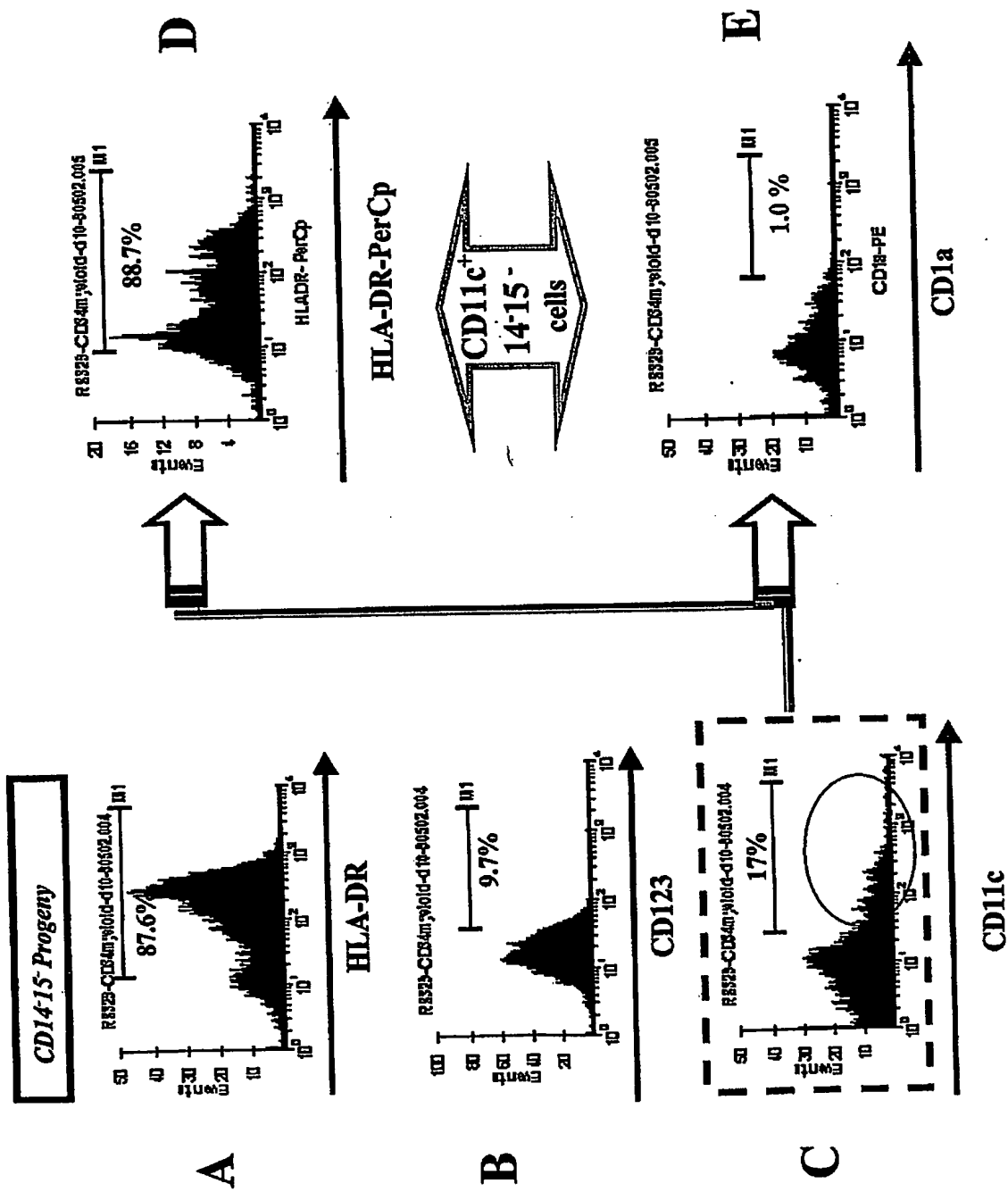


Figure 5

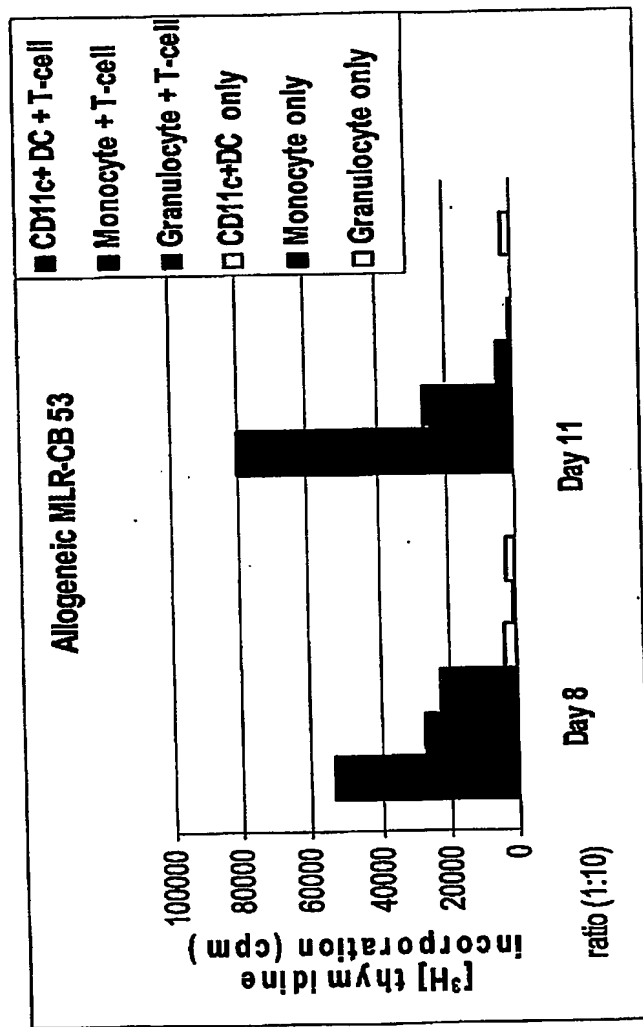
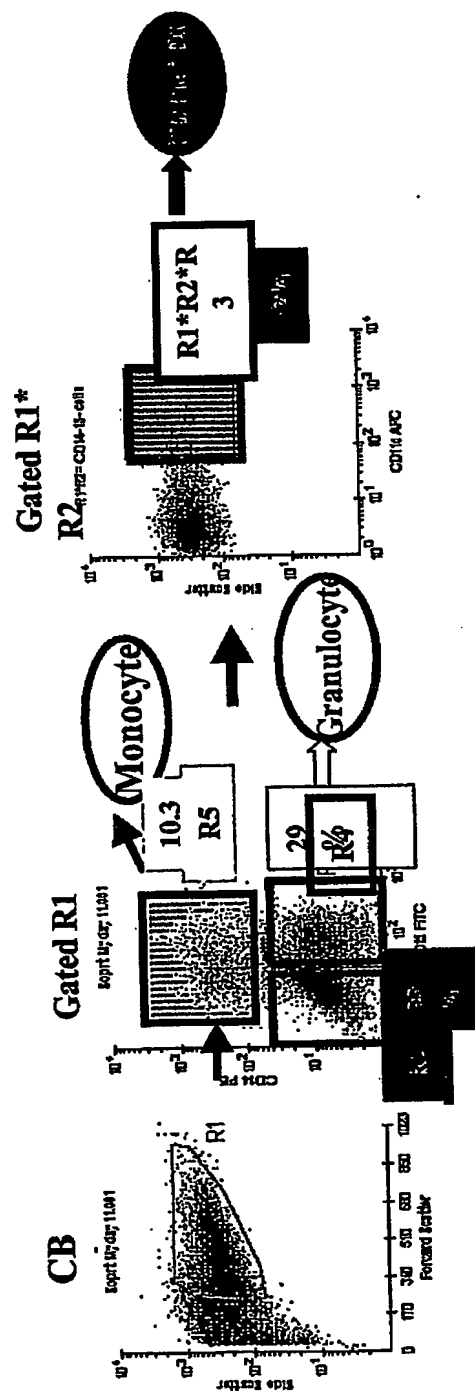


Figure 6

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